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Medical Staff Conference

Uric Acid, Diuretics and the Kidney

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *This Medical Grand Rounds will consider uric acid, diuretic drugs and the kidney, and Dr. David G. Warnock will discuss this topic.*

DR. WARNOCK:† Uric acid is the end product of purine metabolism in humans, and it is excreted by the kidneys.[1,2] This morning I should like to review three aspects of the relationships between uric acid and the kidney: (1) the renal transport mechanisms for uric acid, (2) the effects of hyperuricemia upon the kidney and (3) the clinical setting in which asymptomatic hyperuricemia develops, such as during the treatment of hypertension with thiazide diuretic drugs.

It is generally agreed that at least four components are involved in the renal handling of uric acid.[1,3] These components are summarized in Table 1. The first component is the filtered load of uric acid which is delivered to the nephron. The second component is an avid reabsorptive process which reclaims nearly all of the filtered uric acid load. Another component is a secretory process that provides most of the uric acid which is ultimately excreted in the urine. Last, there is another reabsorptive site which is farther downstream. This last component modulates the final excretion rate of uric acid and may be an important site of action of agents that increase the rate of uric acid excretion in the urine.

Let us consider how much uric acid is presented to the kidney and how much is excreted.[4] The filtered load of uric acid amounts to about 8.5 grams per day if we assume that uric acid is freely filtered. We shall ignore the amount of urate that is bound to plasma proteins (approximately 20 percent). The daily excretion rate for uric acid is normally less than 800 mg. Therefore, there must be an avid tubular mechanism which reabsorbs at least 90 percent of the filtered load of uric acid (Table 2). If normal subjects are loaded with purines to increase the filtered load of uric acid, a tubular reabsorptive capacity of at least 15 mg per minute can be shown.[4] Compare this reabsorptive rate, 15 mg per minute, with the typical filtered load of 6 mg per minute and you can appreciate the large capacity of the kidney for reabsorbing uric acid. This sort of bookkeeping leads us to the realization that there may be a secretory mechanism for uric acid.

The secretory process for organic acids has recently been localized in the middle third of the proximal tubule.[5] The middle third, or the S2

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TABLE 1.—*Renal Transport Mechanisms for Uric Acid*

Filtration
Reabsorption
Secretion
Postsecretory reabsorption

TABLE 2.—*Filtration and Excretion of Uric Acid*

Filtered Load		
(6 mg /dl) × (100 ml/min)	=	6 mg/min
	=	8,500 mg/24 hrs
Excreted	<	800 mg/24 hrs
Tubular Reabsorption	=	7,700 mg/24 hrs
Capacity	=	15 mg/min

segment, is morphologically distinct from the adjacent S1 and S3 segments of the proximal tubule. It is this middle third that has the secretory capacity for organic acids, such as para-aminohippurate (PAH). Its secretory rate is nearly four times that of the adjacent S1 and S3 segments. The secretory site has been described in both the superficial and juxtamedullary proximal tubule. The active step for organic acid secretion is located at the basolateral membrane of the tubule cells.[6,7] The organic acids are actively transported into the cells and accumulate in the interior. They then diffuse into the urinary fluid in the tubule lumen. It is important to realize that many organic acids, such as uric acid, PAH, lactic acid and ketoacids, and drugs, such as diuretics and penicillin, share the same organic acid secretory pathway. These agents can, therefore, compete for access to the active transport site on the blood side of the tubule. The result can be the hyperuricemia that may be seen in lactic acidosis and ketoacidosis and the paradoxical fall in urate excretion that may be seen with low doses of uricosuric agents, such as phenylbutazone, probenecid, salicylates and thiazide diuretic drugs. We shall consider the postsecretory reabsorptive site when we discuss the effects of diuretic drugs on uric acid excretion.

Let us turn to the effects of hyperuricemia upon the kidney. Does chronic asymptomatic hyperuricemia adversely affect renal function? The answer to this question is controversial. Emmerson and Graham Row,[8] in an editorial review replete with anecdotal experience, argue that chronic hyperuricemia causes a primary nephropathy by physical deposition in the renal interstitium and in the lumen of tubules. Superimposed infection, obstruction, calculi and hypertension secondarily contribute to further decreases in renal function. There has even been a specific glomerular lesion described in patients with hyperuricemia.[9] However, when this lesion was closely examined it could not be distinguished from hypertensive glomerulosclerosis.[10] As it turns out, patients with gout whose renal function is compromised are older patients who have hypertension and vascular disease. Furthermore, Rosenfeld[11] has shown in patients followed for three to four years that bringing uric acid concentrations to normal levels in patients with hyperuricemia has no beneficial effect on renal function. Berger and Yü[4] followed 524 patients with gout at intervals of up to 12 years, and in only a few instances were they willing to ascribe diminished renal function to gout. Hyperuricemia alone had no deleterious effects on renal function. Decreased renal function could be ascribed to aging, renal vascular disease, calculi with pyelonephritis, or other nephropathies, including hypertensive glomerulosclerosis. On the basis of their study, it does not seem necessary to treat asymptomatic hyperuricemia to prevent gouty nephropathy.

Let us change our focus from the amount of uric acid in the serum to consider the quantity which is excreted in the urine. There is a form of acute renal failure that can occur in patients with pronounced hyperuricemia and hyperuricosuria. Tubular obstruction by deposits of uric acid is important in the pathogenesis of this form of acute renal failure. This process is typically seen in patients with acute leukemia who are brought into remissions so that there is a huge outpouring of purines from the dying cells.[12,13] Massive urate excretion has also been reported to occur spontaneously in patients with lymphoma. To date, only 50 actual cases have been reported. However, it is important to recognize this form of acute renal failure because it responds dramatically to dialysis. This disorder can be recognized by its abrupt onset in the clinical setting in a patient who has predisposing disease and severely elevated levels of serum and urine urates. It is marked by oliguria and readily responds to dialysis. Forced diuresis and urine alkalinization have not been very successful, so these patients should be dialyzed early. Kelton and co-workers[13] compared five patients with acute uric acid nephropathy with 27 patients with other forms of acute renal failure. The five patients had acute leukemia and an average level of serum urate of 21 mg per dl. These authors made an issue of the urinary uric acid/creatinine ratio,

but this was only a reflection of the pronounced hyperuricemia and uric acid excretion in their patients.[13] There is another clinical setting in which tubular obstruction due to uric acid deposition has been invoked as a contributing factor to acute renal failure. In patients with exertional rhabdomyolysis acute renal failure may develop.[14] However, the hyperuricemia in these patients is modest compared to that in patients with leukemia, so that acute uric acid nephropathy is probably not a very important factor in this form of acute renal failure.

I mentioned the relation between hyperuricemia and hyperuricosuria, seen in its extreme form in patients with acute leukemia. We shall now consider nephrolithiasis. This problem seems to be more clearly related to the level of uric acid in the urine than in the serum. In patients with gout and hyperuricemia, nephrolithiasis can develop, but in most of these patients stones of calcium oxalate form.[15] Furthermore, most patients with established renal disease are hyperuricemic, but only rarely do renal stones develop in these patients. In patients with chronic renal disease, it can be shown that uric acid excretion falls as glomerular filtration rate falls.[8] Therefore, hyperuricosuria is not an important problem in patients with chronic renal insufficiency even though they do become hyperuricemic. When the clearance rate of urate is examined as a function of the glomerular filtration rate (GFR), it is interesting to note that the creatinine clearance rate falls more rapidly than that of urate.[4] As a result, uric acid excretion is relatively enhanced when the GFR is low and the level of serum uric acid is high. The relative enhancement of uric acid clearance rate in renal insufficiency can be explained by the relationship between the level of uric acid in serum and the rate of uric acid secretion. Berger and Yü[4] varied the levels of serum urate over a wide range in normal subjects, in patients receiving allopurinol (who therefore had low levels of serum urate) and in patients with hyperuricemia. They also studied a group of normal subjects who were fed large amounts of RNA to raise the levels of their serum uric acid. In these studies, Berger and Yü[4] estimated the secretory component of uric acid excretion by giving the patients pyrazinamide, an agent that is known to inhibit secretion of uric acid. Their results show that the secretory component assumes increasing importance as the level of serum uric acid increases. This finding explains the relative increase in uric acid clearance rates in patients with hyperuricemia and chronic renal failure. Therefore, we can expect that in some patients with renal failure and hyperuricemia acute gouty arthritis may develop, but nephrolithiasis due to hyperuricosuria will develop only rarely.

The last topic I should like to review is the problem of asymptomatic hyperuricemia that is discovered during a routine screening chemistry examination and the hyperuricemia that develops in patients who receive prolonged treatment with diuretic drugs. Hyperuricemia is a well-known effect of the thiazide diuretics, but it is also observed with more powerful "loop-diuretics," such as furosemide or ethacrynic acid.[16,17] The hyperuricemia seen with diuretic drugs is usually asymptomatic. Does asymptomatic hyperuricemia need to be treated? With regard to chronic gouty nephropathy, the answer is probably no. Lowering the level of serum uric acid will not halt or improve renal insufficiency, as discussed above.[11] With regards to acute gouty arthritis, the answer is also probably no. The Framingham study showed that in only 20 percent of patients with hyperuricemia acute gouty arthritis developed.[18] These episodes were brief and easily treated with nonsteroidal antiinflammatory agents. More importantly, only a fourth of these patients had more than one attack during the 12 years of that study. With regard to nephrolithiasis, the answer is probably no. The important determinant is the amount of uric acid in the urine not in the serum.[15] It is true that secretion of uric acid is enhanced when the level of serum uric acid is high, but this curve was relatively flat in the range of 6 to 9 mg per dl. If there is a tendency in a patient for stones to form, then the amount of uric acid in the urine should be determined.

Coe has reported that 25 percent of patients in whom calcium oxalate stones form excrete more than 800 mg (men) or 750 mg (women) of uric acid per day. He believes that there is a distinct clinical population in whom hyperuricosuric calcium oxalate stones form.[15] The mechanism linking hyperuricosuria to calcium oxalate stone formation is not known, but the incidence of new stone formation in this group does seem to be reduced by allopurinol.[15]

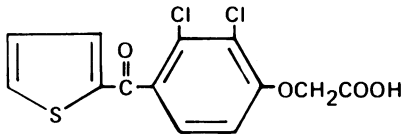
Asyptomatic hyperuricemia can best be managed conservatively. Liang and Fries[19] concluded

that the costs and risks of prolonged drug administration and other practical considerations, such as patient cooperation, mitigate against long-term therapy in asymptomatic patients. In fact, they calculated that the cost of taking allopurinol throughout a lifetime would be approximately $20,000.

How do thiazide diuretic drugs cause hyperuricemia? This question is important insofar as it can tell us something about the function of different parts of the kidney. In addition, a new therapeutic approach will soon be available for patients in whom hyperuricemia develops and who need long-term diuretic drug therapy. Ten years ago it was thought that thiazide drugs raised the levels of serum uric acid by causing volume contraction and by enhancing proximal reabsorption.[1,3] This notion was based upon the observation that replacement of salt and water losses would prevent hyperuricemia.[20] However, since the reabsorptive capacity is normally much greater than the filtered load of uric acid, it is difficult to see how further increasing proximal reabsorption could cause hyperuricemia. It seems more likely that thiazide drugs affect either the secretory process or the postsecretory reabsorptive

TABLE 3.—*Possible Sites of Action of Thiazide Diuretic Drugs*

Proximal Reabsorptive Site
Secretory Site
May blunt secretion, suggested by failure of C_{urate}/C_{inulin} to increase as serum urate is increased
Postsecretory Reabsorptive Site
Analogous to the increased Ca^{++} reabsorption (relative to Na^{+}) which is also seen with thiazide drugs



SK&F 62698 (ANP 3624)

[2,3-dichloro-4-(2-thienyl-carbonyl)phenoxy] acetic acid

Figure 1.—Structural formula for ticrynafen (tienilic acid, Selacryn®). (Reproduced with permission from Okun and Beg.[26])

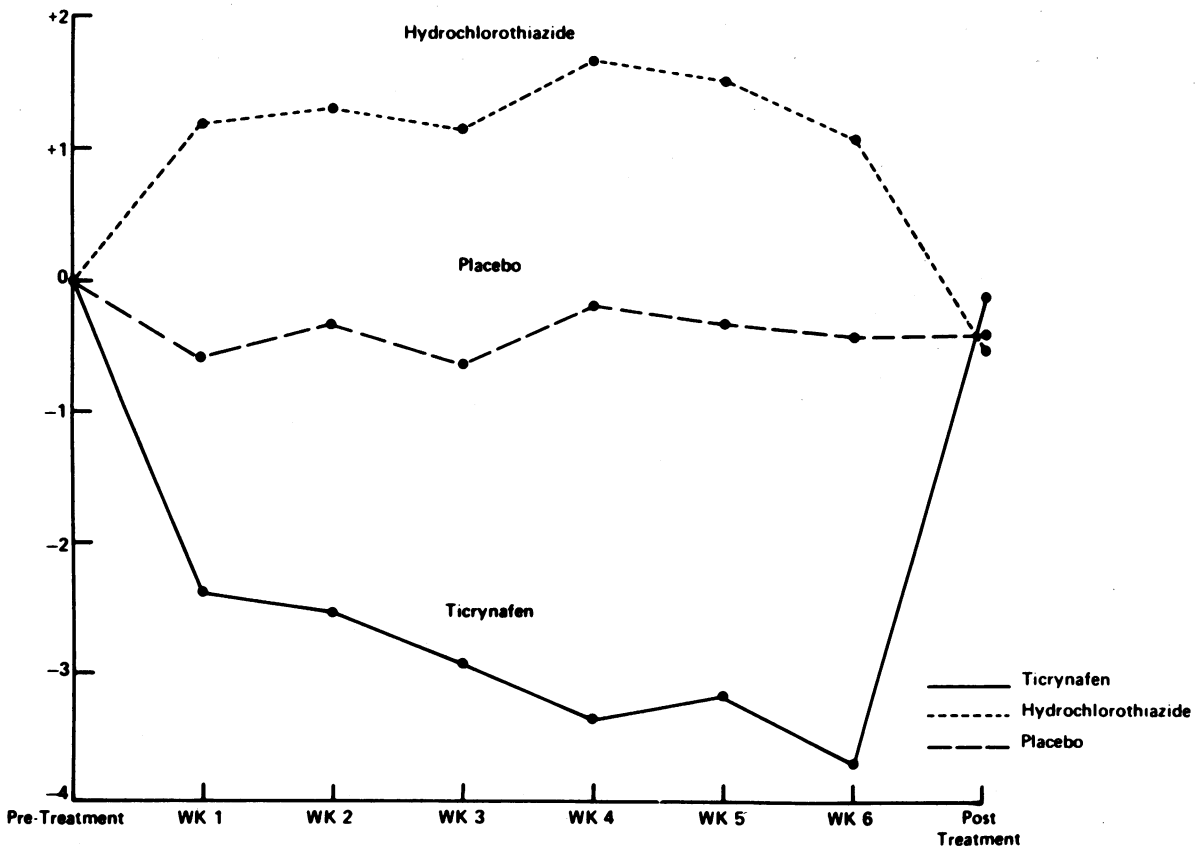


Figure 2.—Changes in serum uric acid. Mean pretreatment values (mg per dl): ticrynafen, 6.3; hydrochlorothiazide, 6.9; placebo, 7.7. (Reproduced with permission from Okun and Beg.[26])

process (Table 3). Blunting of the normal increase in the urate secretion rate together with increased levels of serum uric acid suggest that thiazide drugs affect the secretory process.[17] The postsecretory reabsorptive site is another possible site of action of thiazide drugs. This effect may be analogous to the increase in distal calcium reabsorption relative to sodium reabsorption seen with these diuretic drugs. Blunted secretion or enhanced distal reabsorption would result in an increase in the level of serum uric acid.

A new diuretic drug will shortly become available. Its structural formula is shown in Figure 1. This agent is called tienilic acid in Europe and ticrynafen in the United States (it will be marketed as Selacryn® by Smith Kline & French Laboratories). It is chemically related to ethacrynic acid, but it is not a potent loop diuretic. The renal effects of this drug are nearly identical to thiazide diuretic drugs with one important exception.[21-26] Okun and Beg[26] examined levels of serum uric acid in patients who were treated for six weeks with either hydrochlorothiazide, ticrynafen or placebo (Figure 2). The dotted, upper line shows the results of hydrochlorothiazide treatment, and after six weeks the level of serum uric acid increased nearly 2 mg per dl in these patients. In contrast, the solid, lower line represents a very dramatic fall in the levels of serum uric acid in patients who had received ticrynafen. This fall in the level of serum uric acid with ticrynafen is acutely associated with an increase in uric acid excretion. When compared to thiazides, ticrynafen has also been shown to be an adequate diuretic drug for treating hypertension, at least in short-term crossover studies.[24-26] It may be rational to use this drug in patients with worrisome hyperuricemia, but I should like to emphasize in closing that the worry is more in the mind of the physician than in the patient with asymptomatic hyperuricemia.

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